

**Remarks**

In accordance with the present invention, there are provided novel G-protein-coupled receptor proteins which have high binding affinity for corticotropin-releasing factor (CRF), thus, such proteins are referred to as CRF-receptors (CRF-Rs). In particular, the present claims are directed to human subtypes CRF-RA<sub>1</sub> and a splice variant thereof containing a 29 amino acid insert, CRF-RA<sub>2</sub>. The invention receptor is a principal neuroregulator of the hypothalamic-pituitary-adrenal cortical axis and plays an important role in coordinating the endocrine, autonomic and behavioral responses to stress and immune challenge. CRF-R is functionally coupled to adenylate cyclase as it transduces the signal for CRF-stimulated intracellular cAMP accumulation. The invention CRF-Rs can be employed in a variety of ways, such as, for example, in bioassays, for production of antibodies thereto, in therapeutic compositions containing such proteins and/or antibodies, and the like.

By the present communication, claims 1, 3-7, 11, 13, 15, and 17 have been amended and new claim 20 has been added to define Applicants' invention with greater particularity. Claim 12 is cancelled herein without prejudice as drawn to non-elected subject matter. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the disclosure and the original claims.

Accordingly, after amending the claims as set forth above, claims 1-11 and 13-21 are pending in the application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination, is presented in the Listing of Claims, beginning on page 2 of this communication, with an appropriate status identifier for each claim.

## **I. Priority**

Applicants respectfully disagree with the Examiner's assertion that the earlier-filed applications (e.g., Application Nos. 08/483,139, 08/353,537, and 08/079,320) "do not provide support for SEQ ID NOs: 14 or 15." Applicants further disagree with the Examiner's conclusion that "those claims that make reference to SEQ ID NOs: 14 or 15 are given the benefit of the date of the parent, 09/191,724, 12 November 1998" (Office Action, page 3).

Contrary to the Examiner's assertion, it is respectfully submitted that the claimed subject matter is entitled to a priority date of, at the latest, August 23, 1993, the filing date of earlier-filed Application No. 08/110,286 now U.S. Patent No. 5,728,545 ("the '545 patent"). The present application claims benefit of priority under 35 U.S.C. § 120 or § 365(c) to several applications, including Application No. 08/110,286, filed August 23, 1993.

Claims 13 and 14 are directed to SEQ ID NO:15, an exemplary sequence of hCRF-RA<sub>2</sub>. hCRF-RA<sub>2</sub> is a splice variant of hCRF-RA<sub>1</sub> that includes a 29 amino acid insert located between amino acid residues 145 and 146 of hCRF-RA<sub>1</sub>. SEQ ID NO:15 is fully supported by the disclosure of each of the earlier-filed applications. See, for example, the '545 patent where the following disclosure can be found:

- sequence of SEQ ID NO:2 (amino acid sequence of hCRF-RA<sub>1</sub>), presented at col. 31-34, is identical to SEQ ID NO:2 of the present application;
- sequence of SEQ ID NO:4 (the 29 amino acid insert), presented at col. 35, is identical to SEQ ID NO:4 of the present application; and
- the location of the 29 amino acid insert is specified at col. 28, lines 55-59, i.e., between residues 145 and 146 of hCRF-RA<sub>1</sub>, consistent with the location specified in the present application.

Thus, SEQ ID NO:15 simply shows the sequence resulting from the incorporation of SEQ ID NO:4 between residues 145 and 146 of SEQ ID NO:2. Therefore, SEQ ID NO:15 is fully supported by the disclosures of the earlier-filed applications because all of the sequence

information of SEQ ID NO:15 is represented by the sequences of SEQ ID NOs: 2 and 4 and the description of the location of the insert.

Similarly, claims 1-11 and 15-20 are directed to SEQ ID NO:14, a nucleotide sequence which encodes SEQ ID NO:15. Thus SEQ ID NO:14 merely shows the nucleotide sequence resulting from the incorporation of the nucleotide sequence of SEQ ID NO:3 into the nucleotide sequence of SEQ ID NO:1 between nucleotides 516 and 517. SEQ ID NO:14 is fully supported by the disclosure of each of the earlier-filed applications. See, for example, the '545 patent where the following disclosure can be found:

- sequence of SEQ ID NO:1 (nucleotide sequence of hCRF-RA<sub>1</sub>), presented at col. 29-32, is identical to SEQ ID NO:1 of the present application;
- sequence of SEQ ID NO:3 (the nucleotide sequence encoding the 29 amino acid insert), presented at col. 33, is identical to SEQ ID NO:3 of the present application; and
- the location of the nucleotide sequence encoding the 29 amino acid insert is specified at col. 28, lines 48-53, i.e., as between residues 516 and 517 of nucleotide sequence encoding hCRF-RA<sub>1</sub>, consistent with the location specified in the present application.

Thus, SEQ ID NO:14 is fully supported by the disclosures of the earlier-filed applications because all of the sequence information of SEQ ID NO:14 is represented by the sequences of SEQ ID NOs: 1 and 3 and the description of the location of the insert.

Thus, the sequences of SEQ ID NOs:14 and 15 are fully supported by the disclosure of, for example, the '545 patent. Accordingly, Applicants are entitled to a priority date of, at the latest, the filing date of the '545 patent: August 23, 1993.

## **II. Claim Objections**

Responsive to the Examiner's objection to claims 1-11 and 13-19 for reciting non-elected species, these claims are amended herein to delete reference to non-elected species.

Accordingly reconsideration and withdrawal of this objection are respectfully requested.

### **III. Information Disclosure Statement**

The Examiner's assertion that 2 pages of the information disclosure statement filed on 12 November 2003 allegedly fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 is noted. In response, submitted herewith is a supplemental Information Disclosure Statement and accompanying Form PTO/SB/08 containing the references cited on the allegedly non-compliant 2 pages of the previously submitted IDS. Applicants respectfully request that each reference listed on the presently submitted Form PTO SB/08 be made of record in the present application and that each document be considered by the Examiner.

### **IV. Claim Rejection under 35 USC § 112, Second Paragraph**

The rejection of claims 1-11 under 35 USC § 112, second paragraph as allegedly being indefinite for use of the phrase "suitable stringency" in claim 1 is respectfully traversed.

Applicants disagree with the Examiner's assertion that 'suitable stringency' is allegedly "indefinite, because it does not define clearly the hybridization and wash conditions required, thus leaves open the identity of the nucleic acid sequences that would hybridize" (Office Action, page 4). Contrary to the Examiner's assertion, the meaning of the phrase "suitable stringency" is clear when read in the context of the claim and that which is disclosed in the application and known to those of skill in the art.

The text of claim 1 further defines "suitable stringency" as "allow[ing] identification of sequences *having at least 50% nucleic acid identity* with respect to the reference polynucleotide sequence" (emphasis added). Thus, "suitable stringency" is the stringency required to achieve a minimum level of nucleic acid identity. It is respectfully submitted that one of skill in the art would understand how to adjust hybridization and wash conditions in order to achieve a particular level of identity. Moreover, there is guidance in the specification regarding the level of stringency of hybridization that one would use to achieve a particular level of nucleic acid identity. For example, "low stringency conditions" are described at page 43, line 20 to page 44, 13 as conditions "which allow the identification of sequence which have a substantial degree of

similarity [i.e., at least 50%homology] with the probe sequence.” Low stringency conditions are further described as comprising “a temperature of less than 42.5 °C, a formamide concentration of less than about 50%, and a moderate to low salt concentration.” Exemplary low stringency conditions are also described.

However, in efforts to reduce the issues and expedite prosecution, claim 1 has been amended herein to replace “suitable stringency” with “low stringency,” which is described in the specification with reference to general guidelines and exemplary conditions as discussed above.

Moreover, to the extent that new claim 20 is directed to polypeptides encoded by nucleic acids that hybridize under “moderately stringent conditions” to SEQ ID NO:14, this rejection does not apply. Indeed, moderately stringent conditions are defined in the specification at, for example, page 41, lines 9-22 as conditions “that permit the target DNA to bind a complementary nucleic acid that has about 60% [homology].” Exemplary moderately stringent conditions are further disclosed.

Accordingly reconsideration and withdrawal of this rejection are respectfully requested.

**V. Claim Rejection under 35 USC § 112, First Paragraph (Enablement)**

The rejection of claims 1-6, 8-11, and 13-19 under 35 USC § 112, first paragraph as allegedly failing to meet the enablement requirement is respectfully traversed.

Specifically, Applicants respectfully disagree with the Examiner’s assertion that the specification “does not enable the claimed invention broadly reciting variants and immunogenic fragments of SEQ ID NO:15” (Office Action, page 5). Contrary to the Examiner’s assertion, it is respectfully submitted that the specification fully enables the claimed variants and immunogenic fragments.

In particular, Applicants respectfully disagree with the Examiner’s assertion that “[t]he claims are very broad; the variants as claimed read on a huge group of polypeptides” (Office Action, page 6). Contrary to the Examiner’s assertion the claimed variants embrace a defined group of polypeptides that must meet certain requirements. For example, in claim 1 as currently

amended, contemplated variants must bind CRF and be encoded by DNA that meets the following requirements:

hybridizes under moderately stringent conditions to the complement of the polynucleotide sequence set forth in SEQ ID NO:14,

has at least 60% nucleic acid identity with respect to SEQ ID NO:14.

Thus, contemplated variants are a defined set of polypeptides that bind CRF and are encoded by nucleic acid sequences that are closely related to the exemplary nucleic acid sequences disclosed in the present application.

Applicants further disagree with the Examiner's assertion that "[a]lthough hybridization and wash conditions are recited [in claim 15], the use of open language, 'comprising', allows for the rehybridization and washing at lower stringency, thus many more polynucleotides than those that are complements of SEQ ID NO:14 could potentially hybridize to SEQ ID NO:14" (Office Action, page 6). It is respectfully submitted that this concern is unfounded. The term "comprising" is used with reference to hybridization and wash conditions, not steps in a hybridization procedure, therefore the Examiner's concern regarding the possibility of one conducting a "rehybridization and washing at lower stringency" is not relevant. In order to meet the requirements of the claim, a DNA must hybridize to the complement of SEQ ID NO:14 under the recited hybridization and wash conditions and have the required property of binding CRF. One of skill in the art would therefore readily appreciate that any polynucleotide identified under *lower* stringency conditions would not hybridize under the recited conditions, and therefore would not meet the requirements of the claim with respect to hybridization, minimum percent identity to the reference sequence, and binding CRF.

Applicants further disagree with the Examiner's assertion that "the 'immunogenic fragment' of claim 11 reads on any fragment of the protein, including a peptide consisting of 3-5 amino acids that is capable of inducing a general immune response" (Office Action, page 7). It is respectfully submitted that the immunogenic fragments embraced by claim 11 are a finite group

of polypeptides that are representative of full-length CRF receptors. That is, contemplated immunogenic fragments are those that are capable of eliciting an antibody that will bind CRF receptor. Indeed, the specification teaches that antibodies raised against “a synthetic peptide fragment of the invention protein recognize the synthetic peptide and the corresponding CRF-R on an equimolar basis, and preferably, are capable of inhibiting the activity of the native protein” (see page 34, lines 9-14). Further, it is respectfully submitted that one of skill in the art could readily identify immunogenic fragments using any of a number of available software programs. However, in efforts to reduce the issues and expedite prosecution, the phrase “immunogenic fragment” is amended herein to “antigenic fragment” which the Examiner has acknowledged to be enabled (Office Action page 5).

For at least the reasons above, it is respectfully submitted that Applicants have clearly set forth how to make and use the present invention as required by 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. 112, first paragraph, are respectfully requested.

#### **VI. Claim Rejections under 35 U.S.C. § 102(b)**

**A.** The rejection of claims 1-7, 9-13, and 15-19 under 35 U.S.C. § 102(b) as allegedly being anticipated by Laurent et al. (FEBS 335:1-5, 1993) is respectfully traversed.

The publication date of the Laurent reference is November 29, 1993, the date of that issue of the FEBS journal. However, as discussed above in Section I, the subject matter of the present claims is entitled to a priority date of August 23, 1993, at the latest. Since the Laurent reference was published after the priority date of the present application, it is not available as prior art with respect to the present claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

**B.** The rejection of claims 1, 8, 13, and 14 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen et al. (PNAS 90:8967-71, 1993) is respectfully traversed.

The publication date of the Chen reference is October 1, 1993, the date of that issue of the PNAS journal. However, as discussed above in Section I, the subject matter of the present claims is entitled to a priority date of August 23, 1993, at the latest. Since the Chen reference was published after the priority date of the present application, it is not available as prior art with respect to the present claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

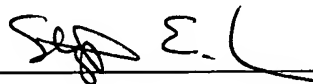
**Conclusion**

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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By



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Enclosure--IDS